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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/838,486	04/07/1997	STEINUNN BAEKKESKOV	02307U-3122	8923

7590 11/04/2002

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	20

DATE MAILED: 11/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/838,486	Baekkeskov et al.
Examiner	**Art Unit**
G.R. Ewoldt	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *10/09/01, 1/29/02, 6/04/02, and 8/14/02*.

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *31, 34, 35, 38-42, 49-59, 62, and 63* is/are pending in the application.

4a) Of the above, claim(s) *38-42* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *31, 34, 35, 49-59, 62, and 63* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 26
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on 6/04/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/838,486 is acceptable and a CPA has been established. An action on the CPA follows.

2. A restriction was required under 35 U.S.C. § 121 in the parent application, as set forth in Paper No. 4 mailed 2/13/98.

Applicant elected Group I, drawn to GAD, and methods of treatment employing GAD, without traverse. This restriction requirement is hereby reiterated.

3. Claims 38-42 stand withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

Claims 31, 34-35, 49-59, and 62-63 are pending and being acted upon.

4. New corrected drawings must be filed with the changes incorporated therein. See the PTO Form 948, mailed 4/28/98. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections. Note that the filing of corrected drawings may no longer be held in abeyance until such time as claims are found allowable. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

5. In view of Applicant's Amendments and Remarks, filed 8/14/02 the previous rejections under 35 U.S.C. 103 have been withdrawn.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 31, 34, 49-53, 58-59, and 62-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for inhibiting the development of IDDM in a NOD mouse comprising administering GAD,

does not reasonably provide enablement for:

a method for inhibiting or preventing the development of IDDM in a patient comprising administering GAD, or a fragment thereof,

for the reasons of record set forth in Paper No. 21, mailed 4/21/01.

Applicant's arguments, filed 12/31/01, have been fully considered but have not been found persuasive. Applicant continues to argue (in several instances throughout the response) that the fact that the FDA has allowed a clinical trial employing the composition and method of the instant claims indicates that a disinterested body of experts has concluded that the trial has a reasonable expectation of success. Applicant is advised that his assertion of what said disinterested body of experts has concluded comprises only attorney's arguments. Said argument cannot be considered evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art. Additionally, the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to

follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration MPEP 2145. Applicant is further advised that regardless of FDA conclusions, the standards for patentability regarding a disclosure enabling the breadth of the claims, as set forth in the MPEP, must still be met. Accordingly, the successful completion of a phase I safety study is insufficient to support the method of the instant claims.

Applicant argues that "the present specification does indicate that care should be taken not to potentiate an immune response. However, general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art at the time of the invention ... either low or high dosages of antigen favor a tolerogenic response whereas intermediate dosages favor an immunogenic response." It is noted however, that Claim 34 recites a method that would encompass low, intermediate, and high dosages (1-500 mg GAD/kg patient body weight). Thus, it appears that Applicant is admitting that at least Claim 34 is not enabled in its breadth.

Further regarding the breadth of the instant claims, none of the claims recite any limitation on the species or strain of the encompassed patient. It is noted, however, that essentially all of the enabling post-filing data (the specification discloses no data in support of the efficacy of the method of the instant claims) was collected using a single inbred animal model, i.e., the NOD mouse. As taught by Atkinson et al. (1999, of record) because the NOD mouse is a highly inbred strain, all experimental animals being genetically identical, results obtained employing said mouse should properly be viewed as results more equivalent to "a single case study in humans," (page 602, column 1). Accordingly, care must be taken in attempting to extrapolate results obtained with the NOD mouse as encompassing all patients. Of record is the reference of Petersen et al. (1997) which specifically teaches that the method of the instant claims does not work in BB rats (*Treatment With GAD65 or BSA Does Not Protect Against Diabetes in BB Rats*). Clearly then the method of the instant claims is not enabled as broadly recited and the post-filing data offered in support of the method of the instant claims cannot enable the claims as broadly recited. Further, *no* evidence of record teaches the absolute prevention of the development of IDDM as recited in claim 62, but rather only the

delay of disease in a highly artificial animal model. It must also be noted that the recitation of a GAD fragment in Claims 62-63 would encompass fragments as small as single amino acids, the administration of which for the inhibition of IDDM would be highly unpredictable.

Further note that more recent attempts to induce tolerance in humans have been completely unsuccessful in at least two different instances. See for example, Marketletter (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) provided successful results in inducing tolerance in animal models, however, both were complete failures in human trials. Finally note that a further recent reference (Goodnow, 2001) flatly states that tolerance induction is unpredictable as many tolerogenic antigens provide both signals that can be both tolerogenic and immunogenic.

Finally, Applicant argues that the BB rat model may be less reliable than the NOD mouse model as a predictor of efficacy in humans. It is unclear then why Applicant has employed a rat experimental model exclusively in the instant specification.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled requirements of paragraphs (1), (2), and (4) of section 3c of this title before the invention thereof by the applicant for patent.

9. Claim 31 stands rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,762,937 (of record), for the reasons of record as set forth in Paper No. 21, mailed 4/24/01.

Applicant has deferred response until such time as the issue of whether or not an interference should be established has been addressed. Applicant is advised that the establishment of an interference will not be considered nor commented upon until such time as all pending claims are in condition for allowance.

10. The following are new grounds for rejection.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 62 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the recitation of "a GAD protein or fragment therefore," is vague and ambiguous. Applicant presumably intended "a GAD protein or fragment thereof."

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 35 and 54-57 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by U.S. Patent No 4,086,142.

the '142 patent teaches a composition in a pharmaceutically acceptable carrier comprising GAD (see particularly, column 4, lines 14-16). Note that GAD comprises the same chemical composition regardless of source.

The reference clearly anticipates the claimed invention.

15. Claims 35, 49, and 54-57 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No 5,762,947.

the '947 patent teaches a composition comprising GAD (see particularly, Example 14). Note that as said composition is clearly intended for *in vivo* administration, i.e., it is referred to as a vaccine, said composition would inherently comprise a pharmaceutically acceptable carrier. The reference further teaches a method for inhibiting the development of IDDM comprising administering lower molecular weight GAD (see particularly Claim 1). Note that lower molecular weight GAD is the only GAD taught by the reference, thus, said GAD would inherently be the GAD of the method of the claim.

The reference clearly anticipates the claimed invention.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c)and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 34, 50-53, and 58-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No 5,762,947.

While the reference does not teach the claimed dosage limitations of 1-500 mg/kg patient body weight, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the dosage of the GAD administered in the method of the reference, said optimization falling well within the purview of one of skill in the art at the time of the invention. Claims 50-52 recite the only well-known sources of protein, i.e., recombinant, synthesized, and natural purified, accordingly it would have fallen well within the purview of one of skill in the art at the time of the invention to obtain the GAD employed in the claimed method from the only three known sources. Additionally, as the point of inhibiting the development of IDDM would have been to keep a patient from developing said disease, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of the claims on a prediabetic, i.e., a patient presumably likely to develop the disease, patient (as recited in Claim 53). Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of the claims employing human GAD65 as said GAD is the actual asserted autoantigen thus it would clearly be preferable to induce a tolerance to the actual antigen. Further, it would have been well-known to one of

skill in the art at the time of the invention that human GAD65 would be incapable of inducing a xenogeneic response which could occur if a GAD65 from another species was used, again rendering human GAD65 the most preferred and accordingly, obvious.

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday from 8:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

G.R. Ewoldt, Ph.D.
Patent Examiner
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November 1, 2002

John J. Doll, Director
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